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(54) Cyclic adhesion inhibitors.

(57) Pharmaceutical compositions comprising at least one cyclopeptide of formulae I (a)-(r)
(a) cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala);
(b) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
(c) cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
(d) cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
(e) cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
(f) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
(g) cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala);
(h) cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly;
(i) cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
(j) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);
(k) cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);
(l) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala);
(m) cyclo(-D-Arg-Gly-Asp-Phe-Val);
(n) cyclo(-Arg-D-Ala-Asp-Phe-Val);
(o) cyclo(-Arg-Gly-Asp-D-Phe-Val);
(p) cyclo(-Arg-Ala-Asp-D-Phe-Val);
(q) cyclo(-Arg-Gly-Asp-Phe-D-Val;
(r) cyclo(-Arg-Gly-D-Asp-Phe-Val);

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or a salt thereof are useful as cell adhesion inhibitors.

This application is a continuation-in-part of application Serial No. 07 909,367, filed July 6, 1992.

Summary of the Invention

The present invention relates to novel pharmaceutical compositions based on cyclopeptides of the formula I(a)-(r):

I

(a) cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala);
(b) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
(c) cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
(d) cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
(e) cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
(f) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
(g) cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala);
(h) cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly);
(i) cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
(j) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);
(k) cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);
(l) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala);
(m) cyclo(-D-Arg-Gly-Asp-Phe-Val);
(n) cyclo(-Arg-D-Ala-Asp-Phe-Val);
(o) cyclo(-Arg-Gly-Asp-D-Phe-Val);
(p) cyclo(-Arg-Ala-Asp-D-Phe-Val);
(q) cyclo(-Arg-Gly-Asp-Phe-D-Val);
(r) cyclo(-Arg-Gly-D-Asp-Phe-Val),

and their physiologically compatible acid addition salts.

The abbreviations of amino acid radicals shown above and below stand for the radicals of the following amino acids:

Ala	Alanine
Arg	Arginine
Asp	Aspartic acid
Gly	Glycine
His	Histidine
Leu	Leucine
Phe	Phenylalanine
Pro	Proline
Val	Valine.

In addition, the following have the meanings below:

BOC	tert.-butoxycarbonyl
CBZ	benzyloxycarbonyl
DCCI	dicyclohexylcarbodiimide
DMF	dimethylformamide
FAB	fast atom bombardment
HOBt	1-hydroxybenzotriazole
M^+	molion peak
OMe	methoxy

The compounds of formula I (a)-(4) and their physiologically compatible acid addition salts are known. They are described in FEBS Lett. 291, 50-54 (1991), the entire disclosure of which is hereby incorporated by reference. In this document, their preparation as well as their conformation analysis is described.

It is known that compounds which specifically inhibit the β_3 integrin receptor ligand interactions ("adhesion receptor antagonist," "ARA") can be used as therapeutic agents for the treatment of osteoporosis, thrombosis, myocardial infarct, arteriosclerosis, inflammations, apoplexy, angina pectoris and tumors. Furthermore, the compounds inhibit cell adhesion in the case of the formation of osteoclasts and are suitable as agents which support angiogenesis and the healing of wounds.

It was a goal of the present invention to find such ARA that can block β_3 integrin fibrinogen binding in order to provide better medicaments for the cited purposes.

Thus, it is an object of one aspect of this invention to provide novel pharmaceutical compositions which can be used as medicaments. Still other objects include methods of effecting pharmaceutical activities.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

Surprisingly, it has been found that the compounds of formula I (a)-(r) and their physiologically compatible acid addition salts have such adhesion receptor antagonistic properties which were not mentioned for these compounds before.

The effect was found by using the method of J.W. Smith, Z.M. Ruggeri, T.J. Kunicki and D.A. Cheresh described in J. Biol. Chem. 265, 12 267- 12 271 (1990).

Details of the method are as follows:

A ninetysix well untreated flat bottom plate was coated with 100 µl/well of 1 µg/ml receptor ($\alpha_{IIb\beta3}$; $\alpha_{v\beta3}$) in coating buffer and incubated on a shaker at 4 °C overnight. The plate was washed 1x with binding buffer and then blocked with blocking buffer (100 µl/well) for two hours at 30 °C. After an additional washing with binding buffer, the biotinylated ligand and the competitor were added.

The ligand fibrinogen was used at a final concentration of 1µg/ml. The competitor was added at increasing concentrations. Both ligand and competitor were added in a volume of 50 µl/well at 2x of the final concentration diluted in binding buffer.

The plate was covered and incubated for three hours at 30 °C. To remove unbound material the plate was washed 3x with binding buffer (100 µl/well).

Goat anti-biotin antibody alkaline phosphatase conjugate (1:2000 dilution) in binding buffer was added (100 µl/well) and the plate was incubated for one hour at 30 °C.

The plate was washed 3x with binding buffer, the substrate solution was added and developed in the dark at room temperature for 1-5 minutes.

The reaction was stopped by addition of 100 µl/well of 0.4 M NaOH and read in the ELISA reader at 405 nm.

All points were run in triplicates.

The following IC 50 values were obtained:

Compound	IC 50 (µM)	
	$\alpha_{IIb\beta3}$	$\alpha_{v\beta3}$
cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala)	0.32	0.90
cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala)	0.76	1.10
cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala)	1.50	0.25
cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala)	0.76	0.31
cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly)	0.13	0.62
cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly)	0.06	0.54
cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala)	22.00	4.50
cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly)	20.50	1.52
cyclo(-Arg-Gly-Asp-Phe-Pro-Gly)	1.53	0.16
cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly)	1.50	1.06
cyclo(-Arg-Gly-Asp-Phe-Pro-Ala)	0.62	0.48
cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala)	0.74	0.37
cyclo(-D-Arg-Gly-Asp-Phe-Val)		
cyclo(-Arg-D-Ala-Asp-Phe-Val)	> 100	52.00
cyclo(-Arg-Gly-D-Asp-Phe-Val)		
cyclo(-Arg-Gly-Asp-D-Phe-Val)	0.60	< 0.05
cyclo(-Arg-Ala-Asp-D-Phe-Val)	> 100	0.77
cyclo(-Arg-Gly-Asp-Phe-D-Val)	0.30	0.05

The invention also relates to the use of the compounds of the formula I and their physiologically acceptable salts for the preparation of pharmaceutical formulations, in particular by non-chemical means. For this purpose, they can be converted into a suitable form of administration together with at least one solid, liquid and/or semi-liquid vehicle or auxiliary and, where appropriate, combined with one or more other active compounds.

The invention also relates to agents, in particular pharmaceutical formulations, containing at least one compound of the formula I and/or one of its physiologically acceptable salts.

These formulations can be used as medicaments in human or veterinary medicine. Suitable vehicles are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical

administration and which do not react with the new compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium, stearate, talc and vaseline. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are particularly used for oral administration, suppositories are particularly used for rectal administration, solutions, preferably oily or aqueous solutions, also suspensions, emulsions or implants, are particularly used for parenteral administration, and ointments, creams or powders are particularly used for topical administration. The new compounds can also be freeze-dried and the resulting lyophilizate can be used, for example, for the preparation of products for injection. The formulation indicated can be sterilized and or contain auxiliaries, such as lubricants, preservatives, stabilizers and or wetting agents, emulsifiers, salts to affect the osmotic pressure, buffer substances, colorants, flavorings and/or aromatic substances. If desired, they can also contain one or more other active compounds, for example one or more vitamins.

The compounds can be employed as pharmaceutical active compounds in human and veterinary medicine, in particular for the treatment and prophylaxis of thrombosis, myocardial infarct, angina pectoris, apoplexy and for tumors, that means cancer diseases.

The invention also relates to the use of the compounds of the formula I for combating diseases, in particular, and to their use for the therapeutic treatment of the human or animal body. In particular, they are inhibitors of cell adhesion, useful to inhibit, e.g., the aggregation of blood-cells and tumor-cells. Thus, the compounds can be used to inhibit adhesion in animal cells, for example, somatic cells or cancer cells of mammals.

The substances according to the invention are as a rule administered in analogy to other known commercially available peptides, but in particular in analogy to the compounds described in U.S. Patent 4,472,305, preferably in dosages of about 0.05-500, in particular 0.5-100 mg per dosage unit. The daily dose is preferably about. 0.01-2 mg kg of body weight. The specific dose for each intended patient depends, however, on many different factors, for example on the activity of the specific compound employed, the age, body weight, general state of health, sex, the diet, the time and route of administration, and the rate of excretion, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Parenteral administration is preferred.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

Preparation example

2.0 g of BOC-Arg-Gly-Asp-D-Phe-Val-Ala-OMe are dissolved in 60 ml of methanol, 1.5 ml of 2 N sodium hydroxide solution are added and the mixture is stirred for 3 hours at 20 °. After evaporation the residue is taken up in water, acidified to pH 3 with dilute HCl and extracted with ethyl acetate. The extract is dried over Na_2SO_4, evaporated again and the BOC-Arg-Gly-Asp-D-Phe-Val-Ala-OH obtained is stirred at 20 ° for 2 hours with 20 ml of 2 N HCl in dioxane. The mixture is evaporated, the H-Arg-Gly-Asp-D-Phe-Val-Ala-OH obtained is dissolved in a mixture of 1800 ml of dichloromethane and 200 ml of DMF and cooled to 0 °, 0.5 g of DCCI, 0.3 g of HOBt and 0.23 ml of N-methylmorpholine are added successively with stirring, and the mixture is stirred for a further 24 hours at 0 ° and 48 hours at 20 °. The solution is concentrated and treated with a mixed bed ion exchanger to free it from salts. This is then filtered off, the solution is evaporated and the residue is purified by chromatography. Cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala) M^+: 646 (FAB) is obtained;

The following are obtained analogously:

cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala); M^+: 660;
cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala); M^+: 646;
cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala); M^+: 660;
cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly); M^+: 632;
cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly); M^+: 645;
cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala); M^+: 646;
cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly); M^+: 632;
cyclo(-Arg-Gly-Asp-Phe-Pro-Gly); M^+: 630;

cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly); M^+ 630;
cyclo(-Arg-Gly-Asp-Phe-Pro-Ala); M^+ 644;
cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala); M^+ 644;
cyclo(-D-Arg-Gly-Asp-Phe-Val); M^+ 575;
cyclo(-Arg-D-Ala-Asp-Phe-Val); M^+ 589;
cyclo(-Arg-Gly-Asp-D-Phe-Val); M^+ 575;
cyclo(-Arg-Ala-Asp-D-Phe-Val); M^+ 589;
cyclo(-Arg-Gly-Asp-Phe-D-Val); M^+ 575;
cyclo(-Arg-Gly-D-Asp-Phe-Val); M^+ 575.

The examples below relate to pharmaceutical formulations which contain the compounds of the formula I or their acid addition salts.

Example A: Tablets

A mixture of 1 kg of cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala), 10 kg of lactose, 6 kg of microcrystalline cellulose, 6 kg of potato starch, 1 kg of polyvinylpyrrolidone, 0.8 kg of talc and 0.1 kg of magnesium stearate is pressed into tablets in the customary manner such that each tablet contains 10 mg of active compound.

Example B: Coated tablets

Tablets are pressed analogously to Example A and are subsequently coated in the customary manner with a coating of sucrose, potato starch, talc, tragacanth and coloring substance.

Example C: Capsules

Hard gelatine capsules are filled with cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala) in the customary manner such that each capsule contains 5 mg of active compound.

Example D: Ampules

A solution of 1 kg of cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly) in 30 l of 1,2-propanediol is subjected to sterile filtration, and ampules are filled with the solution and subjected to sterile sealing. Each ampule contains 2 mg of active compound.

Example D: Ointment

500 mg of cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly) is mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example F: Injections vials

A solution of 100 g of cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly) and 5 g of disodium hydrogenphosphate in 3 l of doubly distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile filtered, filled into injection vials and lyophilized under sterile conditions, and the vials are closed in a sterile manner. Each injection vial contains 5 mg of active compound.

Pharmaceutical formulations which contain one of the other active compounds of the formula I (a)-(q) and/or their physiologically acceptable acid addition salts can be obtained analogously.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

Claims

1. A pharmaceutical composition comprising: at least one cyclopeptide of formulae I (a)-(r) in an amount effective for inhibiting adhesion of animal cells:
   (a) cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala);
   (b) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
   (c) cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
   (d) cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
   (e) cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
   (f) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
   (g) cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala);
   (h) cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly;
   (i) cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
   (j) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);
   (k) cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);
   (l) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala);
   (m) cyclo(-D-Arg-Gly-Asp-Phe-Val);
   (n) cyclo(-Arg-D-Ala-Asp-Phe-Val);
   (o) cyclo(-Arg-Gly-Asp-D-Phe-Val);
   (p) cyclo(-Arg-Ala-Asp-D-Phe-Val);
   (q) cyclo(-Arg-Gly-Asp-Phe-D-Val;
   (r) cyclo(-Arg-Gly-D-Asp-Phe-Val),
   or a physiologically acceptable salt thereof: and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1, wherein said animal cells are somatic cells of mammals.

3. A pharmaceutical composition according to claim 1, wherein said animal cells are cancer cells.

4. A pharmaceutical composition according to claim 1, wherein said composition contains 0.05-500 mg of said cyclopeptide.

5. A pharmaceutical composition according to claim 1, wherein said composition contains 0.5-100 mg of said cyclopeptide.

6. A method for the treatment and prophylaxis of thrombosis, myocardial infarct, apoplexy, arteriosclerosis, inflammations, angina pectoris and or tumors, comprising administering a composition according to claim 1

7. A method according to claim 6, wherein the amount of said cyclopeptide administered daily is 0.01-2 mg/kg of body weight

8. A method of inducing an adhesion-receptor-antagonistic effect in a subject, comprising administering to said subject a composition according to claim 1.

9. A method according to claim 8, wherein the amount of said cyclopeptide administered daily is 0.01-2 mg/kg of body weight.

10. A method according to claim 8, wherein said cyclopeptide is
    cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala;
    cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
    cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
    cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
    cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
    cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
    cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
    cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);
    cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);

cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala)
cyclo(-Arg-Gly-Asp-D-Phe-Val); or
cyclo(-Arg-Gly-Asp-Phe-D-Val)

11. A method according to claim 6, wherein said cyclopeptide is
cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala),
cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);
cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);
cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala),
cyclo(-Arg-Gly-Asp-D-Phe-Val); or
cyclo(-Arg-Gly-Asp-Phe-D-Val)

12. A method of blocking β_3 integrin vitronectin binding comprising administering an effective amount of a cyclopeptide of formula I (a)-(r):
(a) cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala),
(b) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
(c) cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
(d) cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
(e) cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
(f) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
(g) cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala);
(h) cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly)
(i) cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
(j) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);
(k) cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);
(l) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala);
(m) cyclo(-D-Arg-Gly-Asp-Phe-Val);
(n) cyclo(-Arg-D-Ala-Asp-Phe-Val);
(o) cyclo(-Arg-Gly-Asp-D-Phe-Val),
(p) cyclo(-Arg-Ala-Asp-D-Phe-Val);
(q) cyclo(-Arg-Gly-Asp-Phe-D-Val);
(r) cyclo(-Arg-Gly-D-Asp-Phe-Val).

13. A method for the treatment or prophylaxis of osteoporosis comprising administering a composition according to claim 1

14. A method of inhibiting cell adhesion in the formation of osteoclasts comprising administering a composition according to claim 1.

15. In a wound healing composition, the improvement comprising said composition containing at least one cyclopeptide of formula I(a)-(r):
I
(a) cyclo(-Arg-Gly-Asp-D-Phe-Val-Ala),
(b) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Ala);
(c) cyclo(-Arg-Gly-Asp-Phe-Val-D-Ala);
(d) cyclo(-Arg-Gly-Asp-Phe-Leu-D-Ala);
(e) cyclo(-Arg-Gly-Asp-D-Phe-Val-Gly);
(f) cyclo(-Arg-Gly-Asp-D-Phe-Leu-Gly);
(g) cyclo(-D-Arg-Gly-Asp-Phe-Val-Ala);
(h) cyclo(-D-Arg-Gly-Asp-Phe-Val-Gly);
(i) cyclo(-Arg-Gly-Asp-Phe-Pro-Gly);
(j) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Gly);

(k) cyclo(-Arg-Gly-Asp-Phe-Pro-Ala);
(l) cyclo(-Arg-Gly-Asp-Phe-D-Pro-Ala);
(m) cyclo(-D-Arg-Gly-Asp-Phe-Val);
(n) cyclo(-Arg-D-Ala-Asp-Phe-Val);
(o) cyclo(-Arg-Gly-Asp-D-Phe-Val);
(p) cyclo(-Arg-Ala-Asp-D-Phe-Val);
(q) cyclo(-Arg-Gly-Asp-Phe-D-Val);
(r) cyclo(-Arg-Gly-D-Asp-Phe-Val),

or a physiologically acceptable salt thereof.